Decarboxylative Elimination of *N*-Acyl Amino Acids via Photoredox/Cobalt Dual Catalysis

Kaitie C. Cartwright, Jon A. Tunge*

Department of Chemistry, The University of Kansas, 2010 Malott Hall, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States.

Supporting Information Placeholder

ABSTRACT: A dual catalytic strategy for the synthesis of enamides and enecarbamates directly from easily accessible and inexpensive amino acids has been realized. This mild and efficient protocol makes use of an organic photoredox catalyst and a cobaloxime catalyst to achieve decarboxylative elimination using hydrogen evolution to drive the oxidation. Thus, the reaction occurs without a stoichiometric oxidant or the forcing conditions previously employed in attempts to achieve similar eliminations.

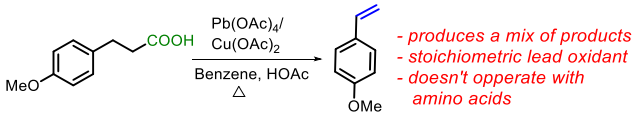
Enamides and enecarbamates possess synthetic utility as stable nucleophilic building blocks in addition to the motif itself being present in biologically active compounds.[1] Methods toward their synthesis include classical protocols such as the acylation of imines, condensation of amines with aldehydes, and through the Curtius rearrangement of acyl azides as well as more modern transition metal catalyzed cross-coupling reactions with amides and activated/stereo-defined olefins.[2] Another appealing route is the direct synthesis of functionally diverse enamides from readily available and inexpensive amino acids.[3] Herein, we describe a noble metal-free procedure that accomplishes the direct conversion of *N*-acyl amino acids to enamides via a sequential radical decarboxylation and hydrogen evolution process facilitated by the cooperation of an organophotoredox catalyst and cobaloxime catalyst. This decarboxylative elimination strategy operates under neutral conditions and bypasses the need for a stoichiometric terminal oxidant and the pre-activation of the carboxylic acid moiety.[4] The marriage of the decarboxylation and hydrogen evolution chemistry has allowed for a mild, operationally simple, and economical route for enamide synthesis.

Kochi pioneered the direct conversion of carboxylic acids into olefins via decarboxylative elimination (Scheme 1A).[5] However, the utility of Kochi's elimination is limited by the requirement of a stoichiometric toxic lead oxidant, often forcing conditions, and significant limitations in scope. Additionally, these reactions tend to produce complex product mixtures.[5,6] Most notably, this elimination was not successful when applied to the α-amino acid substrates of interest to us.[7]

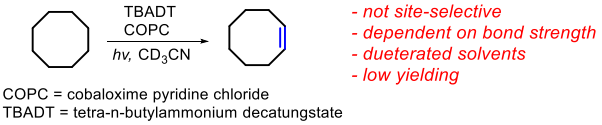
In approaching the decarboxylative elimination of α-amino acids, we were inspired by Sorensen's dehydrogenation of alkanes (Scheme 1B).[8] The dehydrogenation involves hydrogen atom transfer (HAT) to generate an alkyl radical followed by a second HAT reaction to generate the alkene. The need to initiate olefin formation via a hydrogen atom transfer (HAT) reaction limits the reaction scope because it is highly dependent on C–H bond strength and thus, not very selective when many similar C–H bonds are present. Sorensen recognized this limitation and has utilized aldehydes as initiating groups that can be selectively activated due to their low C–H bond strength.[9] We envisioned that olefin formation could be achieved using oxidative decarboxylation to generate a radical intermediate followed by a HAT reaction. Such use of photocatalytic decarboxylation would allow us to site-specifically engage widely-available carboxylic acids in elimination reactions without the need to rely on differential bond strengths. Furthermore, crafting a cooperative catalytic system utilizing a photoredox catalyst and cobaloxime catalyst would allow for enamides and enecarbamates to be directly accessed from *N*-acyl amino acids under mild conditions without stoichiometric oxidants (Scheme 1C).

Scheme 1:

A. Kochi Decarboxylative Elimination

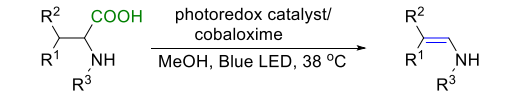


B. Sorensen's Dehydrogenation of Alkanes



COPC = cobaloxime pyridine chloride
TBADT = tetra-n-butylammonium decatungstate

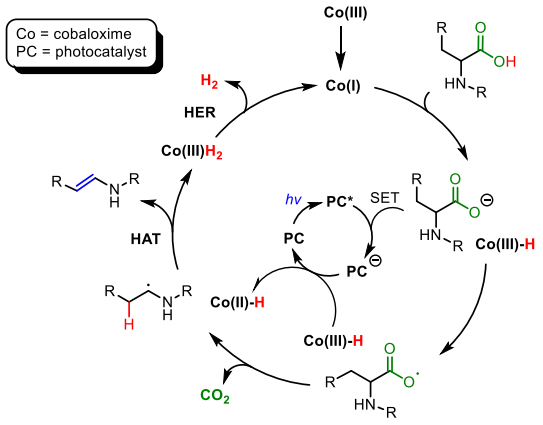
C. Decarboxylative Elimination via Dual Catalysis (This Work)



The decarboxylative elimination was envisaged to be initiated via protonation of a Co(I) species by an α-amino acid (pK_a ~ 2, Scheme 2). It is well-documented that the basicity of Co(I) can be exploited to generate a Co(III)-hydride species (pK_a = 7.7) via deprotonation of common acids.[10] Thus, protonation of Co(I) will provide an α-amino carboxylate. Photo-oxidation of the carboxylate, facilitated by a photoredox catalyst, followed by decarboxylation will furnish an α-amino radical.[11]

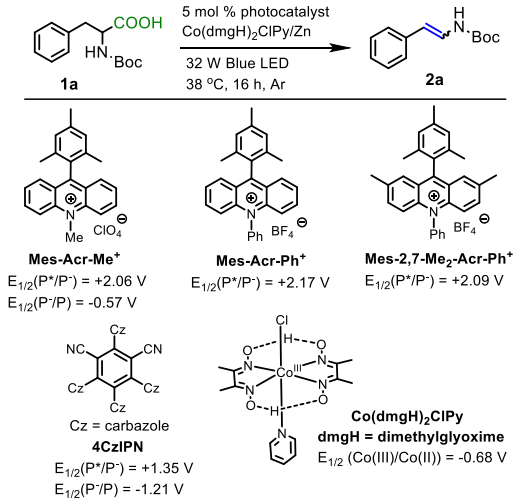
The reduced photoredox catalyst can in turn reduce Co(III) to Co(II), which is an excellent HAT acceptor that targets the weak C–H bonds adjacent to the radical center (Scheme 2).[12,13] This HAT would provide the desired olefin and subsequent hydrogen evolution (HER) would complete the cycle. Ultimately the transformation would produce CO_2 and H_2 as the only stoichiometric byproducts and would utilize visible light as an economical and environmentally friendly energy input.[13]

Scheme 2: Hypothetical Mechanism



To initiate studies, the elimination of *N*-Boc-phenylalanine (**1a**) was investigated using several organic photoredox catalysts combined with commercially available cobaloxime, Co(dmgH)$_2$ClPy (Figure 1). To generate the Co(I) nucleophile, the starting Co(III) was reduced with one equivalent of zinc before being subjected to the reaction mixture. The choice in photoredox catalyst was narrowed down to the Fukuzumi family of acridiniums[15] and the fluorophore, 4CzIPN[16] (Figure 1). These photocatalysts appeared as the logical choices as a result of their favorable oxidation potentials ($E_{1/2}$ = > +2.0 V vs. SCE for acridiniums and +1.35 V vs. SCE for 4CzIPN)[17a,16] for the oxidation of amino carboxylates ($E_{1/2}$ = +0.95 V vs. SCE)[11e] and their lower expense compared to commonly employed iridium photocatalysts. Additionally, a favorable reduction potential for the reduction of Co(III) to Co(II) ($E_{1/2}$ = -0.68 V vs. SCE)[17b] must be considered. In this regard, 4CzIPN has a much more negative reduction potential ($E_{1/2}$ = -1.21 V vs. SCE)[14b] while the common acridinium catalyst (Mes-Acr-Me$^+$) has a more closely matched reduction potential ($E_{1/2}$ = -0.57 V vs. SCE).[17c]

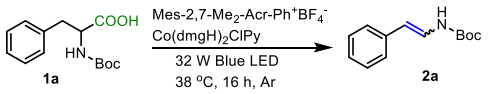
Figure 1: Potential Cooperative Catalysts Screened



Preliminary reactions suggested that the highest conversion towards the desired olefin product was achieved with the acridinium photocatalysts screened (>75% conversion), while poor conversion was observed with 4CzIPN (32% conversion).[18] Of the acridinium catalysts that were investigated, Mes-2,7-Me$_2$-Acr-Ph$^+$ was found to perform the best (95% conversion) and thus was used in further screenings.[19]

Next, the effect of catalyst loading on the decarboxylative elimination was studied. Upon doing so, it became immediately apparent that a slight excess of photocatalyst compared to cobaloxime is vital to the reaction's success (Table 1, entries 1-3). Ultimately, a 3:5 ratio of cobalt to photocatalyst was determined to be optimal. Isolated yields were further increased through a solvent change from acetonitrile to methanol (Table 1, entry 7).

Table 1: Optimization of Catalyst Loadings

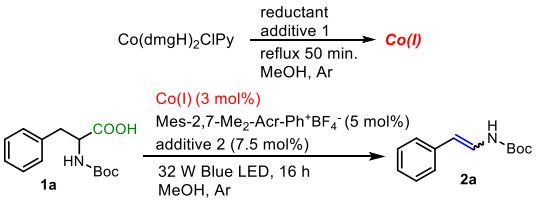


Entry	Co(I)[a] (mol %)	Mes-2,7-Me$_2$-Acr-Ph (mol %)	Solvent	Yield[c]
1	3	3	MeCN	29%
2	3	5	MeCN	57%[d]
3	5	3	MeCN	28%
4	6	10	MeCN	54%
5	1.5	3	MeCN	30%
6	0.75	1.5	MeCN	15%
7	3	5	MeOH	68%
8	3	5	Et_2O	16%
9	3	5	DMF	0%

[a]Co(dmgH)$_2$ClPy reduced with Zn (1 equiv.) and NaCl (3.3 equiv.) in 0.5 mL MeCN. [b]0.2 mmol scale in MeCN (2 mL) under argon. [c]Isolated yields; products isolated as a mix of *E*/*Z*-isomers. [d]Isomer ratio (39:61 E:Z).

Having established the optimal catalyst loadings and solvent choice, the initial reduction of Co(III) to Co(I) was explored. Classically, this reduction had been performed with an excess of sodium borohydride ($NaBH_4$).[10a,20] However, it was hypothesized that any active reductant in the final reaction mixture would interrupt the catalysts' performance.

Table 2: Cobalt Catalyst Optimization



Entry	Reductant (amt.)	Additive 1 (amt.)	Additive 2 (7.5 mol%)	Yield[b]
1	Zn (3 mol%)	NaCl (10 mol%)	-	68%
2[c]	$NaBH_4$ (2 mol%)	-	-	20%
3	$NaCNBH_3$ (7.5 mol%)	-	-	38%
4	STAB (7.5 mol%)	-	-	52%
5	STAB (7.5 mol%)		H_2O	70%
6	STAB (7.5 mol%)	Na_2CO_3 (1 mol%)	-	66%
7	STAB (7.5 mol%)	Na_2CO_3 (1 mol%)	H_2O	82%

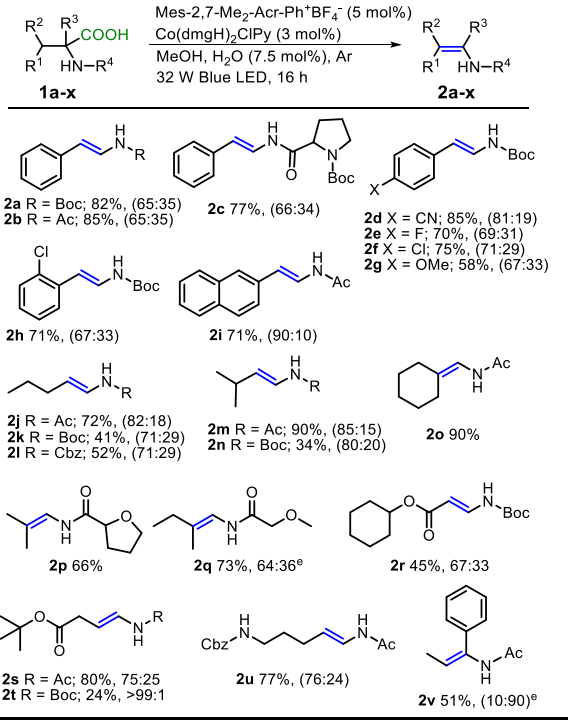
[a]General conditions: Co(dmgH)$_2$ClPy (3 mol%) and reductant refluxed in methanol (0.5 mL) for 50 min. The reduced cobalt catalyst solution was added to *N*-Boc-phenylalanine (0.2 mmol) and Mes-2,7-Me$_2$-Acr-Ph$^+$ (5 mol%) then irradiated with blue LEDs for 16 h under argon. [b]Isolated yields; isolated as a mix of *E*/*Z*-isomers. [c]Reduction performed in acetonitrile.

Thus, the choice in reductant and the amount used in the initial catalyst reduction could impact the success of the elimination reaction. In addition to zinc, $NaBH_4$, sodium cyanoborohydride ($NaCNBH_3$), and sodium triacetoxyborohydride (STAB) were screened (Table 2, entries 1-4). Apart from zinc, STAB provided the highest isolated yield. The use of a catalytic amount of sodium carbonate in the cobaloxime reduction with STAB as well as the addition of water to the reaction solvent further increased the yield (Table 2, entries 5-6). Upon utilizing these additives in conjunction, an 82% isolated yield was achieved (Table 2, entry 7).

In addition to optimization studies, control experiments were also conducted. Only a trace amount of alkene was observed in the absence of photocatalyst and no product was observed in the absence of the cobalt catalyst. While the reaction could be carried out under air, a decrease in yield to 60% was observed under aerobic conditions. Finally, the reaction was found to reach completion in 16 hours with no change in yield upon increasing the irradiation time to 24 hours.

With optimal conditions in hand, a variety of *N*-protected amino acids were investigated for the direct synthesis of enamides and enecarbamates (Table 3). Derivatives of phenylalanine were found to be useful substrates for the elimination (**2a**-**2i**). Interchanging *tert*-butyloxycarbonyl (Boc) and acetyl protecting groups provided similar yields and *E*:*Z* selectivity (**2a**, **2b**). This allows a simple dipeptide to be utilized in the elimination chemistry (**2c**). Additional functionalities on the aryl substituent in the *para* and *ortho* positions were also tolerated and having an electron-withdrawing substituent in the *para*-position provided a slight increase in yield and *E*-selectivity. Conversely, an electron-donating *para* substituent lead to a decrease in yield (**2d**-**2g**).

Table 3: Scope of *N*-Acyl Amino Acids



[a]Reactions were run on 0.2 mmol scale under argon. [b]Cobalt catalyst was reduced with STAB (7.5 mol%) and Na_2CO_3 (1 mol%) in MeOH (0.5 mL) at reflux for 50 min and added via syringe to the reaction mixture. [c]All yields reported are isolated yields. [d]Isomer ratios were determined by ^1H NMR. [e]Major isomer determined by NOESY.

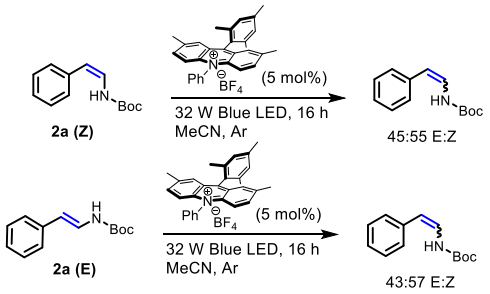
Amino acids other than phenylalanine derivatives provided considerably higher yields when the nitrogen was acylated rather than substituted with a carbamate protecting group (**2i**-**2n**), and unprotected amino acids failed to undergo the reaction. Aside from the protecting group influences, various aliphatic side chains, including those with ester and amine functionalities, led to good to excellent yields of enamides. Additionally, trisubstituted alkenes (**2o**-**2q**) could also accessed through decarboxylative elimination.

To better understand the nature of the observed geometric ratios of products, several additional experiments were conducted. It was speculated that photo-isomerization of the alkenes could be a factor, either through an electron transfer or energy transfer from the photocatalyst to the alkene. Photoisomerizations of this nature have been described by Weaver[21] using iridium photoredox catalysts but have not been previously reported with the acridiniums. To explore this, the *E*- and *Z*- isomers of aspartic acid derivative (**2n**) were independently subjected to the photocatalyst and irradiated in acetonitrile. Indeed, isomerization was observed in each case, producing a steady-state mixture of ca. 45:55 *E*:*Z* (Scheme 3A).[22,23] The same isomerization does not occur upon irradiation in the absence of a photocatalyst or at elevated temperature (50 °C). Taken together, these observations support a hypothesis that the product *E*:*Z* ratios represent the photostationary state of each product under the reaction conditions.

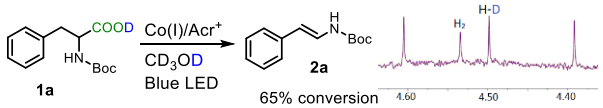
Further mechanistic information was provided by the reaction of *N*-Boc phenylalanine in CD_3OD in a sealed NMR tube (Scheme 3B). Analysis of the crude reaction mixture revealed the formation of H-D and H_2 in a 6:1 ratio. The H-D presumably results from coupling of the exchangeable acid proton (Boc-NHCHBnCO_2D) with the H-atom abstracted in the HAT reaction. Since the exchange of the N-H proton with deuterated solvent is slow under the reaction conditions, the H-D hydrogen could originate from either the N-H or C-H positions α-to the radical. We favor the pathway involving HAT from the C-H bond because we see no evidence for imine formation. Moreover, subjecting a tertiary amino acid, which lacks an N-H bond, to the standard reaction conditions results in product formation (Scheme 3C). Interestingly, the *N*-Me reactant exhibits a high selectivity for the *E*-olefin.

Scheme 3: Mechanistic Investigations

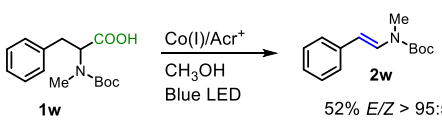
A. Photo-isomerization



B. Reaction Monitored by ^1H NMR Spectroscopy



C. Reaction with Tertiary Amino Acid



In conclusion, a mild and direct decarboxylative elimination of readily available amino acids for the production of enamides and enecarbamates has been realized. This protocol bypasses the use of stoichiometric oxidants, toxic and expensive reagents, and harsh conditions, all of which are seen in related attempts to achieve this transformation. Further explorations into the reaction mechanism and controlling the *E/Z* selectivity are currently under investigation in our lab.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H, ^{13}C NMR spectra, and characterization data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

tunge@ku.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the National Science Foundation (CHE-1800147) and the Kansas Bioscience Authority Rising Star program for financial support. Support for the NMR instrumentation was provided by NSF Academic Research Infrastructure Grant No. 9512331, NIH Shared Instrumentation Grant No. S10RR024664, and NSF Major Research Instrumentation Grant No. 0320648. X-ray analysis was made possible through an NSF-MRI grant CHE-0923449.

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22. The isomerization also proceed to ~80:20 *E*:*Z* in methanol, however, degradation also resulted.

23. For isomerization experiments, 0.04 mmol of each isomer was used and isomerizations were completed under typical reaction set-up as described in SI.

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